Impairment, disability, or handicap in peripheral neuropathy: analysis of the use of outcome measures in clinical trials in patients with peripheral neuropathies

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Abstract

Outcome measures can be classified into measures of impairment, disability, and handicap. To investigate the biological effect of treatment, measures of impairment are appropriate. Studies investigating whether patients benefit from treatment in terms of improvement of functional health, however, require disability or handicap measures.

In a review of the medical literature between 1978 and 1993, 73 controlled intervention studies in patients with peripheral neuropathies were found. Disability or handicap measures were used in two of 54 studies in patients with diabetic neuropathy, in two of six studies in patients with chronic inflammatory demyelinating polyneuropathy, in none of five studies in a mixed group of patients, and in all eight studies in patients with Guillain-Barré syndrome.

The limited use of disability and handicap measures in patients with diabetic and mixed neuropathies can be explained by the experimental nature of most studies. In four of six studies, however, in patients with chronic inflammatory demyelinating polyneuropathy or neuropathy associated with monoclonal gammopathy that were designed to assess effectiveness of treatment, the choice of outcome measures was not appropriate.

It is concluded that in the design of intervention studies in patients with peripheral neuropathy more attention should be paid to a proper choice of suitable outcome measures to assess the effectiveness of treatment.

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Disorders of peripheral nerves can cause weakness and sensory disturbances. Symptoms range from pure sensory to pure motor, and from slight numbness and weakness in patients with chronic idiopathic axonal neuropathy to complete loss of muscle strength including the respiratory muscles in Guillain-Barré syndrome. Therefore, the effectiveness of medical treatment in different neuropathies is assessed by different outcome measures. For example, in diabetic neuropathy there is a focus on sensory signs, which are measured with thermal and vibration perception thresholds, whereas in Guillain-Barré syndrome the focus is on the assessment of muscle weakness.

The choice of an outcome measure should not, however, depend on whether the neuropathy is predominantly sensory or motor. More important is the question the investigator wishes to answer, because this question determines the choice of outcome measures. We made a distinction in two types of questions that can be studied in intervention studies: those that concern the biological effects of a treatment—for example, a phase II study—and those that concern the clinical effects of treatment, in, for example, a phase III study.[1] The second type of questions should preferably be directed to changes in functional health, which is highly relevant for patients.

Outcome measures of clinical trials can be classified according to the model of the consequences of disease developed by the World Health Organisation in 1980.[2] This model describes three classes: impairment, disability, and handicap. Impairment refers to organ dysfunctions or abnormalities of body structure (for example, numbness, weakness, decreased reflexes, or slowed nerve conduction velocity), disability to the patient's functional performance (for example, walking or eating), and handicap to the social disadvantages resulting from impairment and disability (for example, the ability to work). Although this classification seems to be straightforward, there is confusion about terms. For instance, the neurologic disability score is in fact an impairment measure, because it is a composite of cranial nerve function, reflexes, muscle strength, and sensory disturbances.[3]

The purpose of this study was to analyse the choice of outcome measures in intervention studies on peripheral neuropathies.

Material and methods

By means of a Medline search (keywords: peripheral neuropathy and clinical trial, limited to English language, humans, and abstracts) and reference tracing we collected intervention studies published between January 1978 and December 1993.

We ordered the outcome measures used in these studies into pathology, impairment, disability, handicap, and subjective health. Pathology was defined as an abnormality of macroscopic, microscopic, or biochemical structure occurring within the cells of an organ or organ system. This definition is

Table 1 Outcome measures and instruments to assess treatment outcome in studies on peripheral neuropathies, classified in terms of pathology, impairment, disability, handicap, and perceived health

Outcome measure	*Instruments to assess outcome*	*Classification*
Diabetes:		
Nerve biopsy	Histological and immunological studies[21]	Pathology
Signs and symptoms	History and neurological examination findings—for example, weakness, paraesthesia, impaired sensation, loss of tendon reflexes (neurologic symptom score, neurologic disability score), pain (visual analogous scale (VAS), McGill), sleep disturbances[21-71]	Impairment
Symptoms	Scoring of interference with daily activities[25]	Disability
Pain	Scoring of interference with daily and social activities[23]	Disability or handicap
Sensory function	Thermal and vibration perception thresholds, tactile threshold[21 27-32 34-36 39 41 42 44 45 48-50 56 57 60-62 67 69 72-74]	Impairment
Autonomic function	Blood pressure, heart rate, ECG; inspiration and expiration ratio[22 28-30 32 36 41 43 45 47 49 50 56 61 65 69 73 74]	Impairment
Electrodiagnostic features	Conduction velocities, compound nerve action potential[22 24 26 27 29-31 34-42 45 47-50 55-61 66-69 72-74]	Impairment
General perception	Scoring the overall effect of treatment[36-38 46 72]	Perceived health
Cisplatinum neuropathy[75]; uraemic neuropathy;[76 77]; alcohol neuropathy[78]; nutritiona neuropathy[79]		
Signs and symptoms	History and examination[75 76 78 79]	Impairment
Sensory function	Vibration perception threshold[75]	Impairment
Electrodiagnostic features	Conduction velocities, compound nerve action potentials[76-79]	Impairment
Chronic inflammatory demyelinating polyneuropathy[3 6 10 11]; neuropathy associated with monoclonal gammopathy of unknown significance[8]:		
Signs and symptoms	Neurological examination, neurologic disability score, MRC sumscore[3 6-8 10 11]	Impairment
Motor function	Dynamometry, handgrip, maximal fingerpinch[3 6 7]	Impairment
Sensory function	Vibration perception threshold[3 6 8]	Impairment
Electrodiagnostic features	Conduction velocities, compound nerve action potentials etc[3 6-8 10 11]	Impairment
Performance of social activities	Modified Rankin scale[10 11]	Handicap
Guillain-Barré syndrome:		
Signs	Neurological examination, MRC sumscore, muscle weakness score[80-85]	Impairment
Electrodiagnostic features	Conduction velocities, compound nerve action potentials etc[81 86]	Impairment
Mobility and need for care	Functional abilities used in the studies of Hughes and Greenwood; functional testing[80-87]	Disability

synonymous with disease and usually with diagnosis.[4] According to our classification, a nerve biopsy was considered to be a measure of pathology. Neuropathic signs and symptoms (weakness, pain, paraesthesia, numbness, impaired sensation, and areflexia), as well as quantified motor, sensory, and autonomic function tests, and electrophysiological tests were classified as measures of impairment. We considered the need for care and performance of daily activities as measures of disability, whereas social performance scales were regarded as measures of handicap. Finally, scales that assessed the overall subjective effect of treatment were categorised as instruments focusing on perceived health.[5]

Results

We collected 73 randomised controlled intervention studies of which 54 were studies on diabetic peripheral neuropathies, eight on Guillain-Barré syndrome, five on chronic inflammatory demyelinating polyneuropathy, two on uraemic polyneuropathy, and one each on peripheral neuropathy associated with monoclonal gammopathy of undetermined significance, cisplatinum neuropathy, alcohol neuropathy, and nutritional neuropathy. The studies were assigned to four groups: diabetic neuropathies, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, or neuropathy associated with monoclonal gammopathy of undetermined significance, and mixed neuropathies.

Table 1 presents the different types of outcome measures used to assess efficacy. Outcome measures and their instruments are classified in terms of pathology, impairment, disability, handicap, and perceived health.

Table 2 shows the frequency with which the different classes were assessed for the four groups of neuropathies. All studies on patients with diabetic neuropathies, with mixed neuropathies, and with chronic inflammatory demyelinating polyneuropathy focused on the assessment of impairment. In patients with Guillain-Barré syndrome impairment was assessed in six of eight studies. Disability or handicap measures were used in two of 54 studies on patients with diabetic neuropathy, in two of six studies on patients with chronic inflammatory demyelinating polyneuropathy, in none of five studies in a mixed group of patients, and in all eight studies on patients with Guillain-Barré syndrome. Perceived health was scored in five studies on patients with diabetic neuropathy.

Discussion

This current study was undertaken to analyse

Table 2 Frequencies of treatment outcomes in terms of pathology, impairment, disability, handicap, and perceived health in studies on peripheral neuropathies

	Classification				
Neuropathy (n)	*Pathology*	*Impairment*	*Disability*	*Handicap*	*Perceived health*
Diabetes (4)	1	54	1	1	5
Mixed (5)	0	5	0	0	0
CIDP; MGUS (6)	0	6	0	2	0
Guillain-Barré syndrome (8)	0	6	8	0	0

n = Number of studies; CIDP = chronic inflammatory demyelinating polyneuropathy; MGUS = monoclonal gammopathy of unknown significance.

the choice of outcome measures in intervention studies on peripheral neuropathies. The results show that in our reviewed patient groups different outcome measures were used. In patients with diabetes and mixed neuropathies mainly impairment measures have been used to investigate effectiveness of treatment. This is by contrast with studies in patients with Guillain-Barré syndrome, which all used disability measures. Studies in chronic inflammatory demyelinating polyneuropathy or neuropathy associated with monoclonal gammopathy of undetermined significance used either impairment measures or both impairment and handicap measures.

How to explain these differences? First of all, as has been noted previously, there is a difference in questions to be answered—namely, has the treatment a biological effect or a clinical effect? With the second question treatment recommendation is, of course, strongly supported if the concerning intervention is actually improving the functional health of the patients. Treatment in diabetic neuropathy is still in an early experimental stage. The aim in most studies is to investigate if there is any effect at all on the disease process. If there is an effect, however small this may be, this supports the hypothesis that the treatment has some biological effect. Studies such as these increase our knowledge of the disease process itself. To investigate hypotheses about the pathogenesis we therefore need the most sensitive measures because we do not wish to miss even the smallest changes. In these cases impairment measures, which assess disturbed function of peripheral nerves, are the best measures. For as long as there is no satisfactory treatment available in diabetic neuropathy, experimental studies incorporating impairment measures must continue.

In patients with Guillain-Barré syndrome the situation is different. These patients usually improve spontaneously; they may need respiratory support and are unable to walk for some variable period of time. If an experimental treatment showed improved nerve conduction velocities, compound muscle action potentials, or strength, clinicians would immediately ask whether there was a difference in the number of patients who needed respiratory support, differences in time spent on the respirator, differences in time spent in the hospital, or differences in the ability to walk. This kind of information is usually provided by disability measures, which show whether the treatment has a beneficial effect on the patient's functional health. Such information improves clinical decision making.

Yet we do not think that the questions, whether a treatment works biologically or whether it has a clinical effect in terms of functional health, fully explain the use of different outcome measures. In studies on chronic inflammatory demyelinating polyneuropathy and neuropathy associated with monoclonal gammopathy of undetermined significance, all interventions were evaluated with impairment measures, whereas only two studies used handicap scales as well. In the discussion of the results of four studies that focused on impairment measures, the authors did not comment on how results of trials with this kind of measures should be interpreted.[3 6-8] Instead of concluding that the results were encouraging and that other studies, using disability or handicap measures, should be initiated to answer the question whether functional health of patients improves as a result of treatment, treatment recommendations were already presented. The other two studies on chronic inflammatory demyelinating polyneuropathy used the Rankin scale.[9-11] Although the Rankin scale was considered as a measure of handicap,[12] it has a strong association with physical disability.[13 14] Therefore, this scale is not a pure handicap measure. Nevertheless, whether it assesses handicap or disability does not alter the fact that it can be used as an efficient global functional health index.

Just as in the discussion of the results of most chronic inflammatory demyelinating polyneuropathy trials, the differences between impairment and disability or handicap measures remained unnoticed in the published recommendations of the consensus meeting on standards in diabetic neuropathy.[15] In the recommendations emphasis was laid on sensitivity and objectivity of measurements. The authors stressed that because of the relative subjectivity and imprecision of the clinical measures, defined as the medical and neurological history and physical examination, confirmation by more objective measures such as electrodiagnostic, quantitative sensory and autonomic function, or morphometric tests is required. These tests measure pathology or impairment. Objectivity is without doubt important. Objective measurement by electrophysiological methods of, for instance, compound muscle action potentials, may be of less clinical value, however, than a scale scoring the daily activities of a patient, provided that the reliability and validity of such a scale has been investigated and found acceptable. Of the disability and handicap scales, as used in the reviewed studies, only the functional abilities of the Hughes and Rankin scale have been investigated on reliability and validity.[12 16 17] To our surprise, the option of functional measures were not considered in the recommendations of the consensus meeting on standards in diabetic neuropathy. Certainly, from the patient's point of view changes in functional health as a result of treatment are of major importance and should therefore be evaluated. Moreover, the question whether improvement is negatively influenced by side effects of treatment cannot be answered by using impairment scores.

Within other fields of neurology the different levels of measurement outlined have been recognised.[18 19] Most intervention studies in patients with stroke use disability measures these days.[13] The older Matthew scale, which is partly comparable with the so called neurologic disability score recommended for patients with diabetic neuropathy, has been

abandoned. In studies on brain trauma the importance of measuring disability has generally been accepted (for example, the Glasgow outcome scale).[20]

We believe that impairment measures give information on the biological effect of treatment, whereas disability and handicap measures give clinically important and patient relevant information showing whether a treatment improves the patient's functional health. Treatment recommendations should be based on trials in which disability and handicap are assessed, not on trials in which impairment only is assessed. There might be an exception for studies with negative results using impairment measures: if a treatment has no biological effect, it will usually not improve functional health.

In conclusion, in the design of intervention studies in patients with peripheral neuropathies more attention should be paid to a proper choice of outcome measures to assess the effectiveness of treatment.

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